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Malabsorption (Celiac Disease) in Pediatrics

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Malabsorption (Celiac Disease) in Pediatrics

Paul A. di Sant'Agnese, M.D. and William O. Jones, M.D.

In 1888 Gee[24] described a chronic disease of children and adults in London characterized by malnutrition, abnormal stools and a distended abdomen. He named it "celiac disease" from the Greek word for abdomen (Koilio). During the early 1900's Herter[30] in this country wrote extensively on this subject. Thus for many years this disorder was known as Gee-Herter's disease.

In the subsequent 70 years it gradually came to be realized that not one but a group of different disorders were included in the term "celiac disease" in the pediatric age group. These disorders are entirely distinct in etiology, course of illness and ultimate outlook for the patient. However, since they present a common symptom complex resulting in intestinal malabsorption, they resemble each other clinically.

The common defect in this entire group of pathologic conditions is impaired intestinal fat obsorption. The manifestations found in all of these disorders to a variable degree are: (1) malnutrition, (2) foul, bulky, greasy stools, (3) a distended abdomen due to accumulation of improperly digested and inadequately absorbed material and to flatulence, and (4) secondary vitamin deficiencies.

We shall limit our description to the pediatric age group and, for the sake of clarity, to the more severe forms of these various diseases in which the clinical picture is better defined. Admittedly milder patients are seen more commonly than severe ones. However, it is necessary to fully understand the completely manifested disorders in order to be able to diagnose precisely and to treat appropriately the patients who show only some, but not all, of the earmarks of these diverse disease entities.

"Celiac syndrome" and "malabsorption" will be used interchangeably in this paper to indicate the occurrence of the symptom-complex common to all of the disorders in this group.

INTESTINAL FAT ABSORPTION IN CHILDHOOD

Intestinal fat absorption in the pediatric age group presents distinct problems not shared by adult patients with malabsorption.

It is well known that the younger the patient the less the ability to cope effectively with dietary fat. Thus, an otherwise normal premature infant will have steatorrhea on what would be a normal fat intake for an older child. As can be seen from Figure 1, efficiency in handling dietary fat increases during the first few months of life. During the first six months after birth infants present no overt signs of fat intolerance under normal circumstances. The maturation of their intestinal digestive processes, however, is not sufficient to enable them to cope with an additional stress imposed by any serious illness, even if it is from outside the enteric tract. The result is a breakdown in fat absorption, steatorrhea and the symptoms of malabsorption.

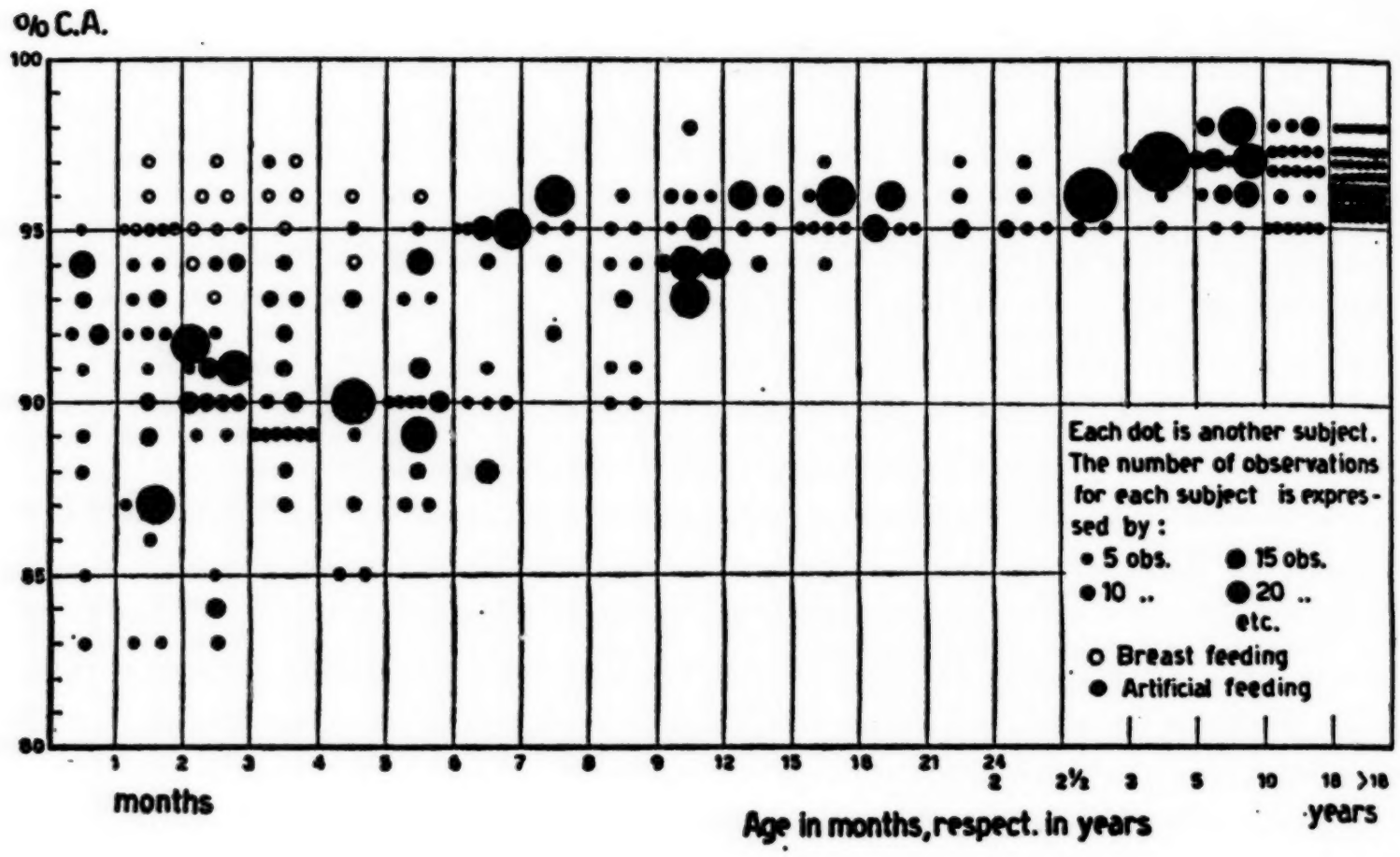


FIGURE 1

Coefficient of fat absorption in normal babies, toddlers, children and adults showing the increase in efficiency of intestinal fat absorption with advancing age. (From: Weijers, H. A. and van de Kamer, J. H.[50])

This breakdown in fat absorption was commonly seen in the case of chronic parenteral infections in the pre-antibiotic era. Even today, anomalies of the genito-urinary tract leading to persistent infection commonly spark the celiac syndrome.

As the child grows older these causes of disturbed intestinal physiology outside the gastro-intestinal tract grow less important. A definite age limit at which these factors are no longer operative cannot be stated, one year of age may be taken as the usual limit before which these influences make themselves felt.

HISTORICAL

The recognition that not one but many diverse disease conditions may give rise to a common symptomatology is recent, as medical lore goes, and is not yet sufficiently appreciated. As a consequence classification and nomenclature of the many disorders leading in children to intestinal malabsorption is a dynamic chapter. It is only recently that some light has been shed on this very confusing field. There are perhaps not many other subjects in pediatrics which have led to so much controversy and skepticism. The widespread and often indiscriminate application of the term "celiac disease" to any child with manifestations of intestinal malabsorption has created this situation. Estimates of its prevalence have ranged all the way from speculation as to its very existence to claims that it has been seen in thousands of patients. A good deal of the pall overlying the subject will be lifted if it is realized that we are dealing in reality with not one, but many different disease entities presenting similar clinical manifestations.

Principal landmarks in this advance of our knowledge of malabsorption in the pediatric age group have been:

1. The recognition of cystic fibrosis of the pancreas as a separate disease entity frequently leading to the symptoms of malabsorption following the reports of Fanconi,[22] Andersen,[4] Blackfan and May,[9] and Harper[29] in the late 1930's.

2. The series of brilliant investigations in Holland by the Dutch group of Dicke,[13] Weijers and van de Kamer[51, 46, 48] in the early 1950's which have led to the appreciation that gluten-induced enteropathy is one of the leading causes of celiac disease in children.

3. The elaboration of the technique of peroral biopsy of the intestinal mucosa introduced by Shiner[43] in England and followed by other authors[39, 11] in an attempt to elucidate the nature of the disturbance and to classify more precisely by histologic and electron-microscopic studies the disorders involved in its genesis.

4. The recent description by Gordon[27, 28] of exudative enteropathy as representing a group of conditions leading at times to intestinal insufficiency.

CLASSIFICATION AND DISCUSSION OF DISEASE ENTITIES LEADING TO MALABSORPTION IN PEDIATRICS

There are many disorders which give rise to the celiac syndrome (malabsorption) in children,[19] as can be seen from Table I.

TABLE I — THE CELIAC SYNDROME (MALABSORPTION) IN THE PEDIATRIC AGE GROUP

Group I

GLUTEN-INDUCED ENTEROPATHY
IDIOPATHIC CELIAC DISEASE
CYSTIC FIBROSIS OF PANCREAS
EXUDATIVE ENTEROPATHY

Group II

Chronic incomplete obstruction or other anatomical abnormalities of intestinal tract (malrotation, stenosis, blind-loop syndrome, fistula, extensive resection of small intestine, etc.)
Chronic parenteral infections (especially genito-urinary tract)
Chronic enteric infections or infestations
Oral antibiotics (especially neomycin)
Lactase, invertase, maltase deficiency
Gastro-intestinal allergy
Acantocytosis

Group III

Tuberculosis of mesenteric glands, hypoparathyrodism, Gaucher's disease, Niemann-Pick's disease, ganglioneuroma, Riley-Day syndrome, biliary atresia, hepatic cirrhosis, ulcerative colitis, regional ileitis

In Group I are listed the main conditions which are associated with the symptoms of malabsorption.

Gluten-induced enteropathy — an unknown basic defect in enzymatic activity or in metabolism that is accentuated or brought to light by ingestion of wheat gluten and leads to impaired intestinal fat absorption and the symptom-complex of the celiac syndrome.

Idiopathic celiac disease or idiopathic steatorrhea—a condition in which the basic metabolic defect is unknown. Although wheat gluten is not a factor in the genesis of the symptoms abnormal intestinal fat absorption with all of its attendant consequences is present.

Cystic fibrosis of the pancreas — a generalized disease of exocrine gland function[17] in which pancreatic insufficiency and perhaps other factors lead to intestinal malabsorption.

Exudative enteropathy — presumably not one but a group of pathological conditions. It leads to excessive loss of serum protein through the gastro-intestinal tract and to steatorrhea and malabsorption in the cases with abnormalities of intestinal lymphatics[49].

Other disorders which may give rise to the same symptom complex are listed in Table I under Groups II and III. In Group II are enumerated conditions which *frequently* give rise to malabsorption whereas diseases that *on occasion* give rise to these symptoms are enumerated in Group III.

It is not possible within the limits of this review to describe in detail all of the conditions which give rise to malabsorption in children. We shall, therefore, concentrate on some of the main disorders causing the celiac syndrome.

I. IDIOPATHIC CELIAC DISEASE AND GLUTEN-INDUCED ENTEROPATHY

Definition

In celiac disease there is an unknown basic defect in enzymatic activity or in metabolism which leads to impaired intestinal fat absorption and the symptom complex of the celiac syndrome.

From recent investigations[13, 19, 23, 2] it has become apparent that in the majority of cases in the pediatric age group ingestion of wheat gluten accentuates the basic defect and leads to the clinical manifestations of malabsorption. The etiology is recognizable on the basis of sensitivity to wheat and rye gluten; the disease in such cases should be called, "gluten-induced enteropathy."

In the remaining patients in which wheat gluten is not a factor in the genesis of symptoms but in which abnormal intestinal fat absorption with all its attendant consequences is present, the disease still must be called "celiac disease" or "idiopathic steatorrhea" until more is known about its pathogenesis.

These two conditions have an identical clinical picture and will be discussed together in the first part of this chapter.

Onset

The great majority of pediatric patients presenting this symptomatology are infants between the ages of 6 and 12 months. Older textbooks usually state that celiac disease does not start until the end of the first year or later. Nevertheless, more recent findings[6] in this country show that the onset of some of the symptoms frequently occur in the very first few weeks or months after birth. However, it is not until after the age of 6 months that the combined occurrence of

malnutrition, a distended abdomen and abnormal stools make the diagnosis clear. It appears, based on statistical analysis, that breast feeding delays and at times prevents the appearance of manifest symptoms. Thus, the earlier onset of celiac disease may be caused by the much greater use of artificial feeding in recent years.

"Celiac Crisis"

Patients who for weeks or months after birth gain weight irregularly but who have periods of abnormal stools and occasional vomiting may suddenly manifest the severe symptoms of the so-called "celiac crisis." An acute or chronic infection usually acts as the triggering mechanism that brings to light the symptoms which were in abeyance up to that time.

Symptoms of the "celiac crisis" are large and watery stools, frequent copious vomiting, and a markedly distended abdomen caused by intestinal loops being filled with fluid and gas. Roentgenograms show a condition similar to that of intestinal obstruction. This episode of acute dehydration and electrolyte depletion usually presents an acute medical emergency. It is a severe threat to the patient's life. The first urgent need is to restore the depleted fluid and electrolyte reserves by intravenous administration of fluid. In severe cases steroid therapy may be life-saving.

"Celiac crises" rarely occur in persons after two years of age. This probably is an expression of the greater stability of the water and electrolyte balance in older children and adults.

Physical, Laboratory, and Roentgenographic Findings

The clinical and laboratory symptoms of the fully manifested and severe celiac disease are well known and adequately described in all textbooks.[37]

Severe malnutrition, large foul, bulky stools, a distended abdomen, flat buttocks and poor muscular tone are present. Secondary effects of various vitamin deficiencies also may be found. In former times, vitamin D deficiency rickets was common because of the large amounts of this lipo-soluble vitamin lost through the stools. There usually is a microcytic hypochromic anemia and a hypoproteinemia with the albumin fraction mostly affected. Other laboratory signs of intestinal malabsorption usually present are: a flat glucose tolerance test, low or absent serum carotene and increased fecal fat content on balance studies.

The total serum protein level is an important indication of severity of the disease; in infants, it is an indication of impending crisis. In our experience, "celiac crisis" with sudden dehydration and acidosis does not occur if the serum protein level remains normal. A level of total serum protein below 5.0 gm/100 cc indicates an unstable balance which can be easily upset by an intercurrent upper respiratory or other infection.[6]

A so-called "deficiency pattern" of small intestinal motility on x-ray gastrointestinal series is always present. Excessive segmentation of the barium column, coarsening and obliteration of the mucosal folds, clumping and coarsely granular flocculation are present in varying degree. On occasion hypertonicity and hypermotility are found instead of hypotonia and hypomotility. It should be stressed

that changes in small intestinal motility on roentgenography are not as significant in children as in adults. Many other conditions, such as allergy, fright, and cold may give rise to similar pictures in the pediatric age group. The presence of such changes, therefore, is an expected but not a diagnostic finding.

The physical appearance of such patients is quite distinctive: a sad and fretful face, a distended abdomen, flat buttocks, and skin hanging in folds because of the wasting of subcutaneous tissue and poor muscular tone.

The Natural History of Celiac Disease

Patients put on rigid diets devoid of all forms of starch have an excellent clinical response in the great majority of cases.[14, 15] In patients with gluten-induced enteropathy similar gratifying recovery can be expected by excluding only wheat and rye gluten and limiting the oral intake of fat.

After initiating dietary therapy there is a time lag of several weeks before clinical improvements are evident. This is followed by a *period of rapid improvement* lasting from 6 to 18 months. During this second stage patients put on weight rapidly and improve markedly insofar as the character of the stools is concerned. The gain in weight, however, is apt to be much more rapid than the gain in height and the little patients often become slightly obese at this stage.

The patients then continue to improve. When examined several years after their original admission, however, they still are found to have many abnormal laboratory tests, especially the ones related to fat absorption, even though clinically they look quite well.[14] At this time they are in a *"latent stage"* in which, despite their normal appearance and clinical well-being, their chemical processes are still abnormal.

In former times, occasionally young patients were seen in whom improvement did not take place and the severe disease persisted unaltered into adult life. This sequence of events does not usually occur because of our improved and more effective methods of treatment.

Relation of Celiac Disease in Children to Sprue in Adults

Many adults with so-called adult celiac disease or non-tropical sprue not only have a clinical and laboratory picture almost identical to children with this condition, they also have a history of celiac disease in childhood or a family history of this disorder.[45, 15] It was concluded, therefore, that in many instances celiac disease in children and sprue in adults are the same condition; that is, both are the same basic metabolic defect brought to light by a variety of triggering mechanisms (dietary deficiency, intestinal infection, psychological trauma, etc.) even though expressed somewhat differently in the diverse age groups.

The Role of Wheat and Rye Gluten

The role played by wheat and rye gluten in the genesis of clinical symptoms in the majority of children with celic disease, demonstrated by Dicke, Weijers and van de Kamer[13] in Holland, confirmed in a more precise manner the surmises that such was the case. In Figure 2 it can be seen how the feeding of wheat flour

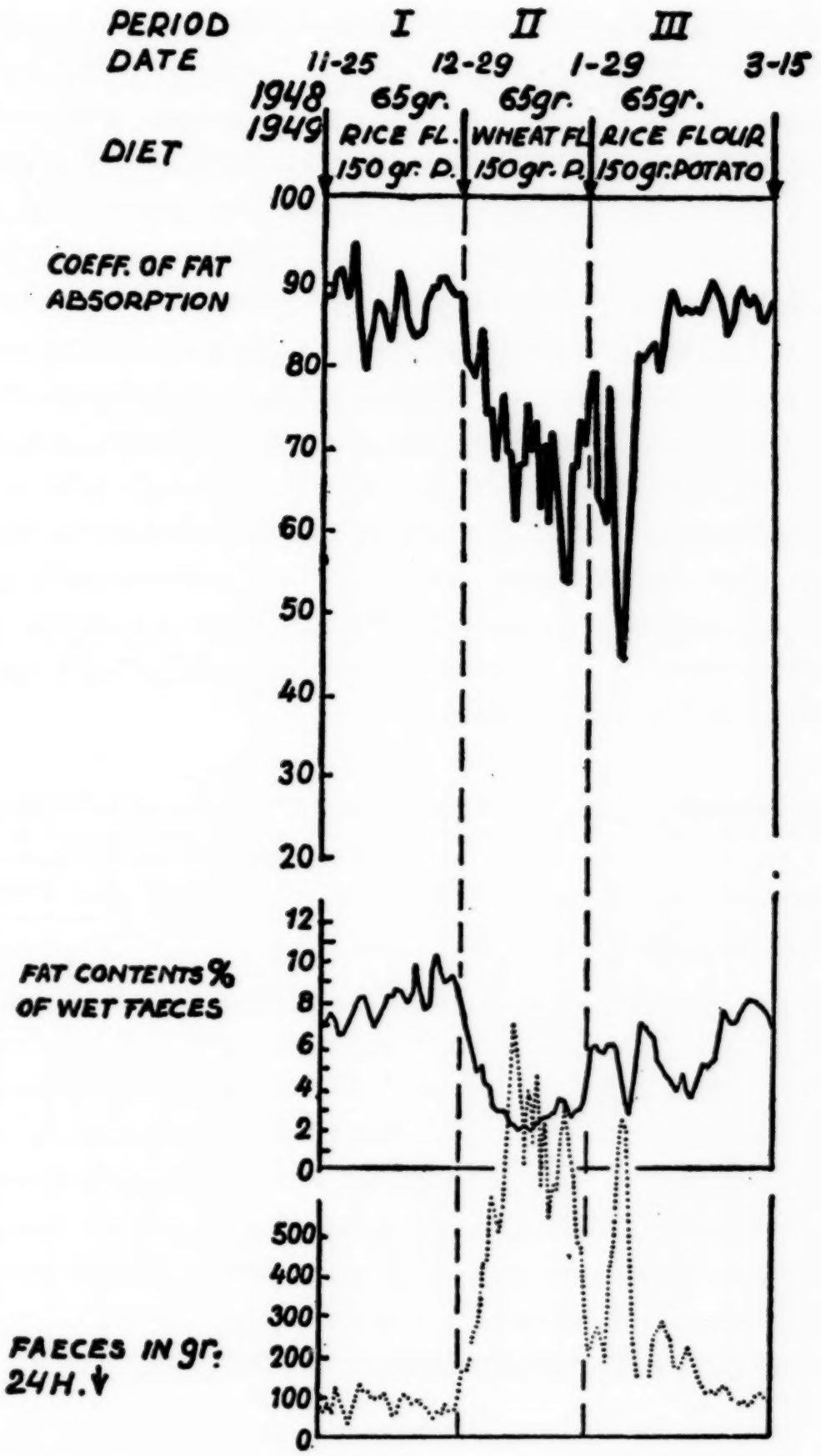


FIGURE 2

The adverse effect of the introduction in the diet of wheat flour on the coefficient of fecal fat absorption and on the volume of stools in a patient with gluten-induced enteropathy. (From: Dicke, W. K., Weijers, H. A. and van de Kamer, J. H.[13])

has an adverse affect on patients with celic disease, both as to their symptomatology and more specifically to their degree of steatorrhea. The fecal fat content increases markedly and consistently when wheat flour is administered and, at the same time, the volume of the stools increases significantly. Further investigations by the same researchers,[51, 46, 48] which soon were confirmed by others in England[2] and various parts of Western Europe, demonstrated that the offending factor in wheat flour was gluten. Gluten, the protein portion of wheat flour, accounts for about 10% of the total weight of wheat flour.

Wheat gluten, because of its solubility in alcohol, can be easily divided into two fractions: glutenin and gliadin. Gliadin, it soon became apparent, is the factor responsible for most of the celiac symptoms. Furthermore, the Dutch investigators observed that glutamine is a major component of wheat gliadin and accounts for 47% of its weight. They found that when this amino acid is destroyed by chemical means, gliadin can be administered to patients without any adverse affects being noted (Figure 3). Many different foods were then analyzed. It was found that foods containing a high glutamine content, notably wheat gliadin and glutenin and rye gluten, are the ones responsible for most of the symptoms of celiac disease. The great majority of foods, they found, do not have a high enough content of this amino acid to cause adverse effects when ingested by patients sensitive to these compounds.[48] However, when the amino acid glutamine was administered "as such" to patients with gluten-induced enteropathy, it did not have an adverse effect.[48] They concluded that glutamine must be in combination with other compounds as a polypeptide to reproduce the harmful effects of the clinical disease.

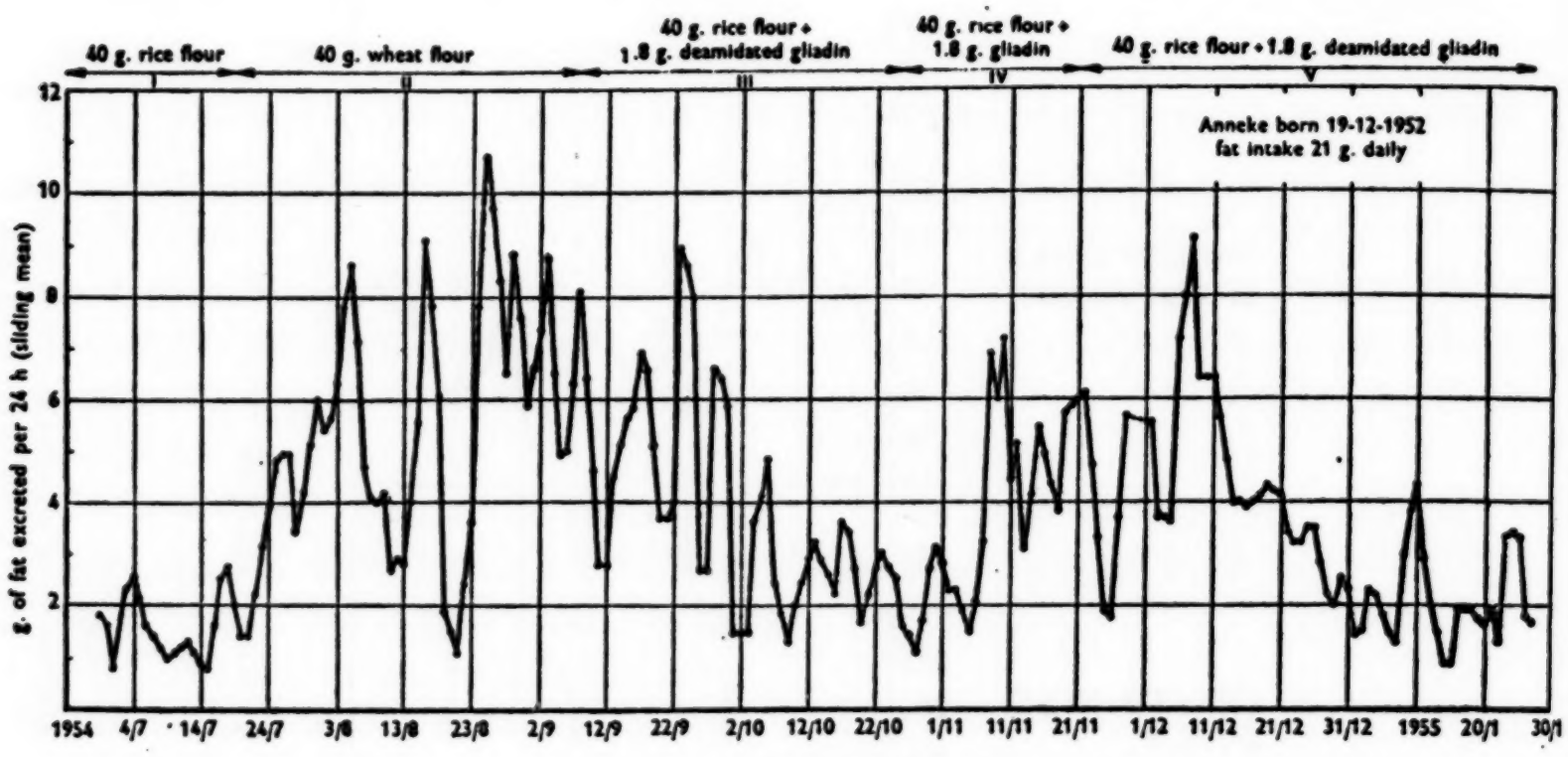

40 g. rice flour
40 g. wheat flour
40 g. rice flour + 1.8 g. deamidated gliadin
40 g. rice flour + 1.8 g. gliadin
40 g. rice flour + 1.8 g. deamidated gliadin
I
II
III
IV
V
Anneke born 19-12-1952
fat intake 21 g. daily
g. of fat excreted per 24 h (sliding mean)
12
10
8
6
4
2
1954 4/7 14/7 24/7 3/8 13/8 23/8 2/9 12/9 22/9 2/10 12/10 22/10 1/11 11/11 21/11 1/12 11/12 21/12 31/12 1955 20/1 30/1

FIGURE 3

Excretion of fecal fat in patient with gluten-induced enteropathy on diets containing rice flour, wheat flour, rice flour with added gliadin and rice flour with "deamidated" (destroyed chemically) gliadin. (From: van de Kamer, J. H. and Weijers, H. A.[48])

Some conclusions can be drawn from these findings which are quite in agreement with our present day concept that in celiac disease there is an unexplained error in metabolism which is present whether the symptoms are manifest or not. Dicke, Weijers and van de Kamer were led to their classic investigations by the observation that a marked increase in the incidence of celiac disease occurred in Holland during World War II when the occupying German forces introduced wheat as the main staple of food. This evidence indicates that the basic metabolic defect was present in many Dutch children prior to World War II but was dormant until brought to light by the introduction of gluten in the diet.

Our own experience, previously mentioned, re-enforces the error in metabolism

theory of celiac disease. Many of the children who later presented celiac disease had symptoms shortly after birth and before they were given potentially harmful cereals or other foods containing wheat gluten. What other explanation is forthcoming but that in such cases there is an error in metabolism which is inherently severe enough to give rise to symptoms even though no gluten is administered?

In addition, it should be noted that in the past the attentions of investigators always was polarized on intestinal fat absorption, as the primary defect in this disorder as exemplified by the name "idiopathic steatorrhea" used interchangeably in former times with celiac disease or sprue. However, from the soon confirmed investigations of the Dutch group, it became obvious that disturbed fat absorption was in reality a secondary manifestation induced at will by the introduction of gluten in the diet. Thus they proved it to be merely a clinical expression of the basic metabolic defect.

What then is the basic defect? This question must remain unanswered as yet, as investigations have failed to lead to definite conclusions.

Incidence

Both severe gluten-induced enteropathy and severe idiopathic celiac disease have become increasingly rare in this country and in Western Europe in the last few years. Presumably this reduced incidence is because of our better knowledge of nutritional requirements and the advent of effective antibiotic agents, which prevent the chronic infections that so often used to act as the trigger mechanisms in initiating the clinical manifestations. In the mild form, however, disturbances of intestinal absorption in children related to ingestion of wheat or rye gluten are not uncommonly seen in office practice. As the outstanding clinical symptom is intolerance to dietary starch, these patients were called at times in the past "starch intolerant."[5] These patients respond very satisfactorily to appropriate dietary treatment. But if our concept is correct, the basic metabolic defect lies dormant in many children and adults and awaits the proper conditions in order to manifest itself, at least insofar as gluten-induced enteropathy is concerned.

Peroral Small Intestinal Biopsies

Further light has been shed on this obscure but fascinating subject by the development of the peroral biopsy originally introduced by Shiner[43] in England and taken up subsequently by many investigators.[39, 11, 3, 40] Histologic changes in celiac disease and sprue were never consistently found at necropsy, presumably because of the autolytic changes which occur in the intestinal tract soon after death. Thus, the peroral biopsy method was devised to obtain freshly biopsied intestinal mucosa. Although initially conceived primarily as an aid in the morphologic diagnosis of intestinal disease, it is certain to afford momentous advances in the understanding of the physiology and biochemistry of the normal and diseased intestinal mucosa.

Most of the experience to date with gluten-induced enteropathy has been in adults and to a much lesser extent in children. In this disorder the mucosa is abnormal. It has a flattened mucosal surface, blunting, fusion or absence of the

villi, diminution of the surface goblet cells and increase in plasma cells, eosinophils and polymorphonuclear leukocytes in the lamina propria.

These mucosal changes in the intestinal tract are consistently found in cases of gluten-induced enteropathy; they are not found in the normal intestinal tract. The true specificity of the findings, however, is yet to be established, particularly in view of the close similarity to the appearance of the small bowel in neomycin toxicity[21] and in other conditions leading to malabsorption.

The reversibility of the changes in gluten-induced enteropathy is also a matter of some controversy.[39, 3, 40] It appears that reversibility is variable; some patients have had definite return of their mucosal changes to normal, while others have not. Further, it seems reasonable that the severity and duration of ingestion of gluten and the length and severity of the resulting enteropathy might well lead to irreversible damage to the intestinal mucosa. The age and duration of the disease in patients may well be important factors in the histologic appearance.

It is clear that interpretation at this stage is difficult. Much further study is needed, especially in the pediatric age group in order to further define the significance of these findings. However, these changes have led some investigators to speculate that the basic defect in gluten-induced enteropathy may consist in a congenital and hereditary deficiency in the enzymatic processes responsible for digestion and absorption at the intestinal mucosal level.

In the pediatric age group the best success has been achieved with the use of the multipurpose suction biopsy tube described by Brandborg, Rubin and Quinton.[11] The tube is passed orally in the fasting state under mild sedation and under fluoroscopy through the pylorus and into the duodenum. Evidence to date[39, 3] indicates that the distal duodenum is a satisfactory site for the purpose of characterizing the changes in celiac disease. Current thinking, because of trauma and radiation exposure involved in passing the tube beyond the ligament of Treitz, prefers the distal duodenum as the site for biopsy. Experience may prove that biopsy of the jejunal mucosa is preferable for selected purposes.

II. CYSTIC FIBROSIS OF THE PANCREAS

Definition and General Considerations

Cystic fibrosis of the pancreas is a generalized hereditary disease of children, adolescents and young adults and is due to dysfunction of exocrine glands.[17, 44] In fully manifested cases there are chronic respiratory disease, pancreatic insufficiency, abnormally high concentration of sweat electrolytes and, on occasion, cirrhosis of the liver. The involved organs may be affected in varying degree leading to marked differences in the clinical picture.

No histologic changes are found in exocrine glands which do not secrete mucus, such as eccrine sweat, parotid and tear glands. The chemical composition of their secretions, however, is abnormal and shows marked increase in electrolyte concentration. The basic pathologic change in mucus producing glands consists of an accumulation of abnormal viscid secretions with consequent dilatation of the secretory gland. These findings may be present throughout the body, but give

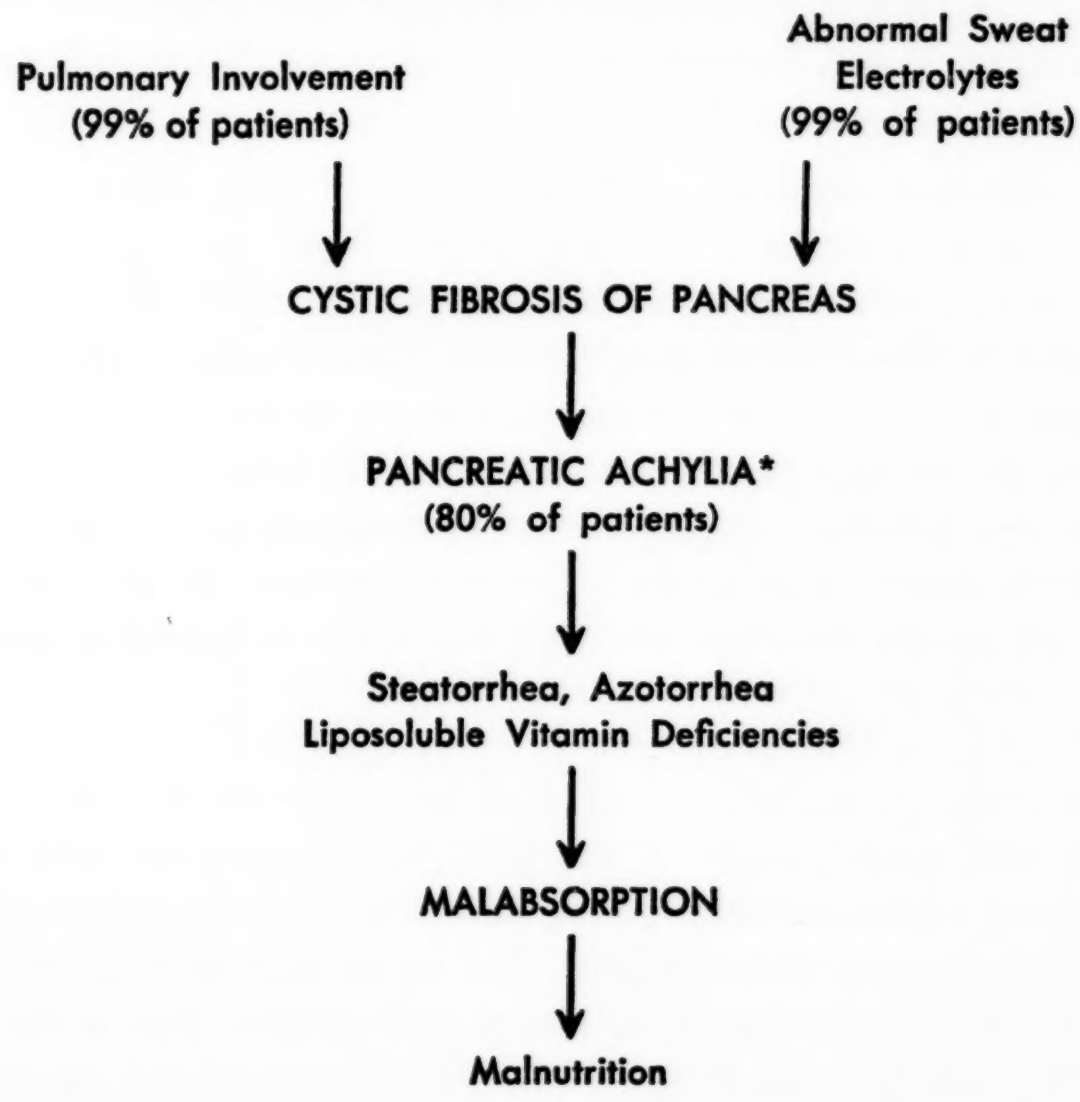
rise to symptoms only when organs such as the lungs, pancreas and liver are involved. The most striking pathologic manifestations are found in the pancreas of patients in whom this organ is involved. These manifestations attracted the attention of the early investigators and gave the disease its name. In the pancreas amorphous eosinophilic concretions obstruct the large and small ducts, with consequent dilatation of the acini and degeneration of the exocrine parenchyma which is replaced by fibrous tissue and eventually by fat. The islands of Langerhans appear normal.

Pancreatic Deficiency and Malabsorption

Cystic fibrosis is not a disease of the pancreas but is one in which this organ is frequently, though not necessarily, involved. Pancreatic achylia is present in 80% of patients and pancreatic function is normal or slightly reduced in the other 20 per cent.[16] The presence of normal amounts of pancreatic enzymes on duodenal assay and the absence of steatorrhea, creatorrhea and the other manifestations of intestinal malabsorption do not *per se* negate the diagnosis if other signs of the disease are present, namely, abnormally high sweat electrolyte levels and chronic pulmonary disease.

The most common gastro-intestinal symptoms of cystic fibrosis are due to pancreatic achylia (Table II) and the consequent intestinal malabsorption.[18] The

TABLE II — PANCREATIC INSUFFICIENCY AND CONSEQUENT MALABSORPTION IN THE GENERALIZED DISEASE: CYSTIC FIBROSIS OF THE PANCREAS



***All pancreatic enzymes are absent**

absence of pancreatic trypsin, lipase and amylase leads to impaired absorption of fats, proteins, and to a lesser extent, carbohydrates. Steatorrhea and creatorrhea are marked. Although patients with pancreatic deficiency do not tolerate an increased dietary intake of fats, they are able to handle satisfactorily large amounts of oral proteins thus making possible a positive nitrogen balance. The stools are bulky, offensive, and at times greasy. Malnutrition may be marked despite an apparently adequate dietary intake. The appetite is frequently ravenous.

A large amount of the fat-soluble vitamins is lost through the stools. Vitamin A deficiency was seen in patients with this condition many years ago, but in recent times its manifestations have rarely been noted. Serum levels of vitamin A are almost invariably normal, although those of the vitamin A precursor, carotene, in the same patients are low. This apparent discrepancy is presumably due to the relatively large amounts of preformed vitamin A given to children. Massive subcutaneous bleeding associated with hypoprothrombinemia due to vitamin K deficiency occassionally is encountered. Rickets have almost never been seen in cystic fibrosis, a fact which is difficult to explain. Lack of growth has repeatedly been cited as the reason for this lack of vitamin D deficiency symptoms. This explanation is unsatisfactory since growth in this disease, while frequently retarded, may be almost normal at times even in the face of marked steatorrhea. Gordon and Nitowsky[26] have shown that fibrocystics with pancreatic achylia are deficient in vitamin E and exhibit a creatinuria that ceases on administration of this dietary supplement. Blanc and co-authors[10] have confirmed pathologically the widespread presence of ceroid pigment, associated with vitamin E deficiency, in the smooth muscle in all necropsy cases above the age of three years. Oral administration of vitamin E does not, however, seem to make a significant difference in the clinical status of these patients.[34]

Recently intestinal absorption studies with I^{131} have been performed.[38] Adults with acquired pancreatic deficiency do not absorb neutral fats adequately, but do show normal serum curves of the isotope after injection of tagged fatty acids. Patients with fibrocystic disease, however, do not seem to absorb normally either preparation. This leads to the suspicion that a factor other than pancreatic deficiency may be at fault in the malabsorption in cystic fibrosis. The recent demonstration of a difference in the structure of mucopolysaccharides in duodenal contents of fibrocystics[20] leads to the belief that secretions in many and perhaps all intestinal glands are abnormal and thus contribute to intestinal insufficiency.

Incidence

In contrast to severe gluten-induced enteropathy and severe idiopathic celiac disease, patients with cystic fibrosis of the pancreas are observed with increasing frequency among adolescents and young adults, as well as infants and young children. In former years these patients died in infancy or early childhood of broncho-pneumonia or occasionally of severe malnutrition. Due to the introduction of effective anti-bacterial drugs, better dietary control and increased diagnostic ability, the life span of patients with cystic fibrosis has increased greatly.

Cystic fibrosis is now the most frequent cause of severe malabsorption in the pediatric age group.[17]

III. EXUDATIVE ENTEROPATHY

Hypoproteinemia caused by leakage of serum protein into the intestinal lumen and the subsequent elimination of protein from the body has recently been described as a specific entity[27, 28, 42, 31] of exudative enteropathy, as well as an associated finding in other well-defined diseases, including ulcerative colitis and regional enteritis.

These patients have abnormal losses of protein and fat into the intestinal tract, along with edema, emaciation, intermittent diarrhea, and less frequently anemia and recurrent infection. Striking depression of serum albumin and globulin occurs and rapid disappearance of these substances from the serum has been demonstrated.

Gordon[27] has developed a method for determining the presence of leakage of protein into the intestinal lumen. Radioiodinated PVP (Polyvinylpyrrolidone), a plasma-protein substitute with a molecular weight approximating that of albumin, is injected intravenously; then urine and stools are collected for determination of radioactivity. Thereby, one can assess the degree with which the injected material passes into the intestinal lumen. Up to 1.5% of the injected PVP has been collected in the stools of control subjects whereas the stool recovery in patients with exudative enteropathy has ranged from 2.5 to 35% (Figure 4).

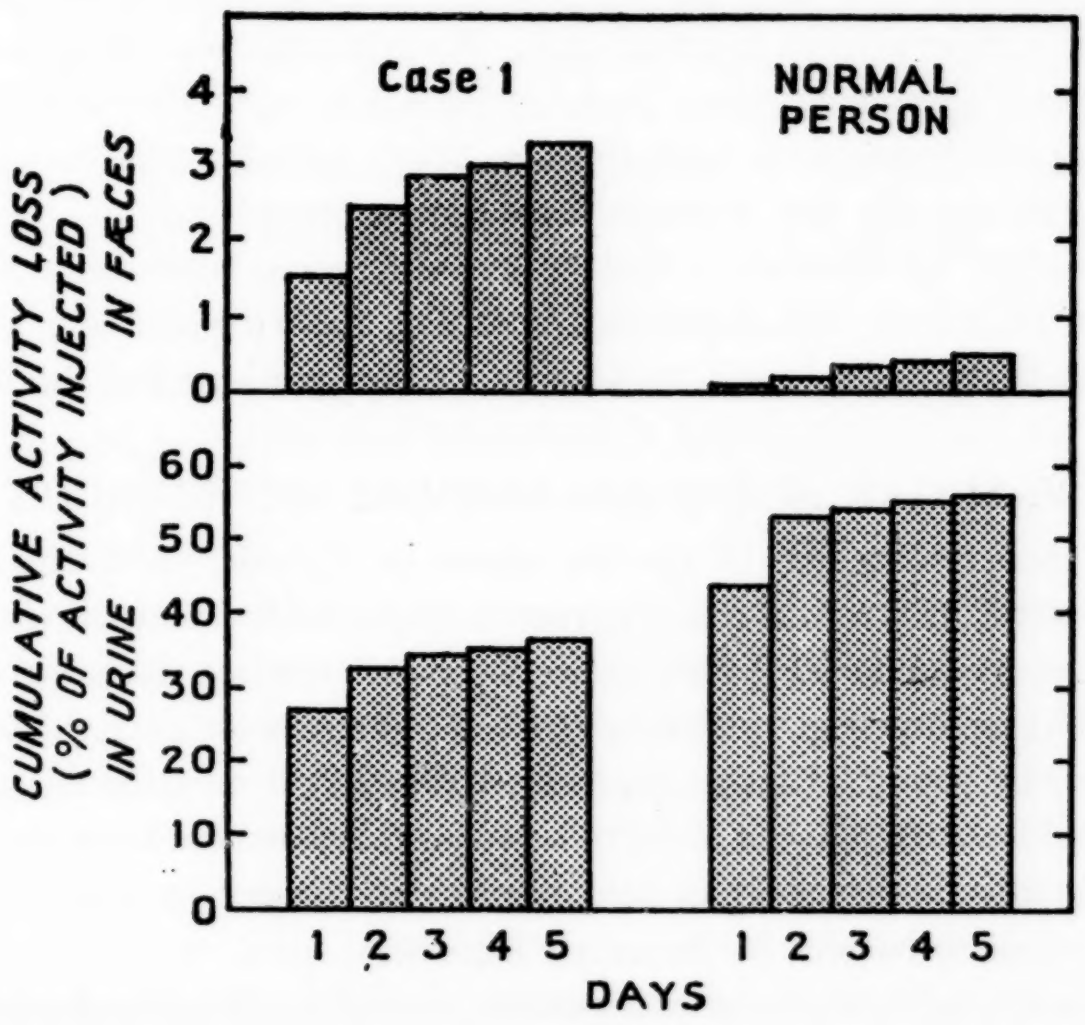


FIGURE 4

I^{131} labeled PVP (polyvinylpyrrolidone) excretion in feces and urine in a patient with exudative enteropathy (case 1) and a normal person. (From: Schwartz, M. and Jarnum, S.[42])

Dilatation of mesenteric lymphatics has been found in some of the patients, especially the children.[49] Thus, it is felt that lymphatic leakage, possibly secondary to lymph channel obstruction, might explain the leakage of protein and fat in certain patients.

IV. GASTRO-INTESTINAL ALLERGY

There are many reports in the literature that gastro-intestinal allergy causes the celiac syndrome.[33, 12] Indeed it has been known for many years[1, 35] that in many infants antibodies are found in circulation against different foodstuffs in the weeks following the introduction of the new staple in the diet — e.g., eggs, etc. Only in some instances do these antibodies give rise to clinical sensitivity through the antibody-antigen reaction, the earmark of allergy. Presumably this reaction occurs only in individuals which have what has been called an "atopic constitution" and who, therefore, are predisposed to develop the manifestations of allergy.

In our experience during many years of observation and search, rarely have we found cases in the pediatric age group in which we were firmly convinced that gastrointestinal allergy was the cause of chronic diarrhea. We have observed patients with acute gastro-intestinal symptoms due to hypersensitivity to a food material (vomiting, cramps, acute diarrhea), but we usually have not been able to incriminate with certainty one specific food in the genesis of chronic nutritional disturbances. It is far too common that infants presenting these symptoms, and later proved to have gluten-induced enteropathy or cystic fibrosis, are thought to have allergy to cows' milk. A variety of hypoallergenic formulas are then tried without success. Such patients are not hypersensitive *to,* but intolerant *of,* modified cows' milk protein. Much valuable time would be saved if allergy were not the first etiologic explanation considered.

Nevertheless, we advocate a trial of hypoallergenic formulas and of special diets when indicated. We deprecate, however, the frequent use of the term "allergy" to cover one's failure to find the correct etiology for the disturbance.

V. SUGAR SPLITTING ENZYME DEFICIENCIES

The ever-increasing list of specific causes of chronic, recurrent diarrhea in association with failure to thrive has recently been added to with the reports of Holzel, Schwarz and Sutcliffe[32] and Weijers, van de Kamer, Dicke and Ijsseling.[32] These investigators have described patients with a celiac-like syndrome characterized by abnormal frequent, loose, bulky bowel movements, poor weight gain, irritability, and enlarged abdomen. In these patients the basic defect appears to be an absence or deficiency of one or more of the enzymes necessary for the hydrolysis of disaccharides in the small intestine.

It is known that complex carbohydrates, including the disaccharides, are not absorbed as such. They must be split into their component monosaccharides which then can be absorbed intact from the intestinal lumen into the portal venous system. Although one enzyme, amylase, is adequate to split many forms of starch

into the disaccharide maltose, other specific enzymes (maltase, lactase or invertase) are necessary for the final hydrolysis of their respective disaccharides. The mechanism of this type diarrhea can be explained as follows: The unsplit disaccharides pass unabsorbed to the large bowel where they are fermented by the normal bacterial flora. The products of the fermentation include the lower organic acids, primarily lactic acid and acetic acid, resulting in a lowered stool pH and large bowel irritation.

Holzel, *et al.*[32] described two siblings who failed to thrive in infancy because of their inability to metabolize lactose. In these patients a lactose tolerance test led to no rise in blood glucose or galactose whereas a glucose plus galactose tolerance test led to a normal rise in blood glucose and galactose. Both patients responded to a diet containing sucrose and glucose and devoid of lactose. Weijers[52] reported that he saw diarrhea in children due to the absence of one or more of the sugar-splitting enzymes — invertase, maltase and lactase. Sucrose and maltose tolerance tests revealed failure of digestion of the respective disaccharides and a striking elevation of stool lactic acid content was demonstrated. These patients responded to omission of the offending sugar from the diet or to addition of the lacking enzyme.

These reports are of great interest both because they alert us to the possibility of previously unrecognized specific etiologies of chronic diarrhea and failure to thrive and because they suggest that similar enzyme deficiencies may play a role in the malabsorption associated with other intestinal disorders including, possibly, gluten-induced enteropathy. It is further tempting to speculate that such deficiencies might exist in a mild and transient form in some cases of "idiopathic infantile colic". Further study of these and other conditions with appropriate carbohydrate tolerance tests and evaluation of stool pH and lactic acid would seem indicated.

VI. ACANTHOCYTOSIS

A new syndrome which presents another form of celiac disease was first described in 1950 by Bassen and Kornzweig.[8] Most, but not all, of these patients have been Jewish and/or products of consanguineous marriages. Only a few cases have been reported to date.

"Acanthocytosis" is the term used to designate these patients — The reason: one of the unusual features of this disturbance is an abnormal appearance of red blood cells. The erythrocytes have the appearance of well-used cogwheels — the outer margins taking the form of rounded or sharp pseudopods, giving the cell a crenated appearance. The authors agree with Salt, *et al.*[41] that a better name for this disorder is a-β-lipoproteinemia since acanthocytosis is only one of many bizarre findings in these patients and the evidence now available suggests that the basic metabolic defect concerns an inability to form β-lipoprotein.

The striking clinical findings are: (1) a celiac syndrome with abnormal bowel movements, steatorrhea, and failure to thrive appearing in infancy or early childhood and (2) a central nervous system disease characterized by retinopathy

of a dengenerative, pigmented type and ataxia suggestive of spinocerebellar damage appearing in late childhood or early adolescence.

Pertinent laboratory abnormalities, in addition to the red blood cell changes described above, are increased fecal fat, absent or very low serum carotene, and low serum vitamin A, cholesterol, total lipid and phospholipid; failure of increase in serum turbidity or total lipid after a fatty meal; and absence of serum β-lipoprotein. Study of the parents and paternal grandfather of one patient,[8] revealed the presence of one-half the normal amount of β-lipoprotein and diminished serum levels of cholesterol, total lipid and phospholipid but with no other clinical or laboratory findings confirmatory of the apparent homozygotic state.

The nutritional manifestations of this disorder have been improved by administration of a low-fat diet. The ocular and neurologic changes have been progressive in some patients, but have remained stationary in others.

This rare disorder appears to be an inborn error of metabolism and the responsible gene transmitted as an autosomal recessive. The basic defect is as yet not precisely defined. The most reasonable explanation to date is that the abnormalities of the red blood cells and of the ocular and central nervous system are secondary to defects in intestinal fat absorption and systemic fat transport and that these defects are due to or associated with the inability to synthesize β-lipoprotein.

A-β-lipoproteinemia should be suspected in any child presenting the celiac syndrome and in any patient with a history of celiac disease who develops signs of ocular or spinocerebellar degeneration. The diagnosis can be made on the basis of steatorrhea, low serum lipids and the demonstration of acanthocytes.

DIFFERENTIAL DIAGNOSIS OF MALABSORPTION IN THE PEDIATRIC AGE GROUP

There are several tests to establish the presence of malabsorption and to assess its degree. While it is not within the scope of this review to give any detailed summary of such investigations, the results indicating impairment of intestinal fat absorption are as follows:[19, 23, 15]

Serum carotene is low or absent (valid only if children are old enough to take carotene in their diet), as this lipochrome is poorly absorbed in the presence of steatorrhea. The average *fecal fat excretion* on three or four day stool collection (a shorter period gives unreliable results) is markedly increased. Oral glucose tolerance test is generally flat, although more irregular in character in children than in adults. *Vitamin A tolerance test* is expected to be low in the presence of steatorrhea but is not advised because its results are too irregular. *Xylose tolerance test* and *intestinal absorption of fats tagged with* I^{131} may be useful in the future but normal figures are not available for children as yet. *Roentgenographic examination* for study of small intestinal motility shows the so-called "deficiency pattern." This is an expected occurrence but

cannot be used to establish the diagnosis in the absence of other findings because there are many other causes which may give rise to a similar x-ray picture in children, e.g., cold, hunger, allergy and fright. Changes in small intestinal motility are, therefore, less reliable in the pediatric than in the adult age group.

In addition, intestinal infection and infestation, parenteral infections, chronic incomplete obstruction of the intestinal tract and all the many other disorders, listed in Groups I and II of Table I, which may give rise to intestinal malabsorption in the pediatric age group will have to be excluded by appropriate methods, e.g., stool cultures, roentgenographic examination of gastro-intestinal and genito-urinary tract, etc.

If the etiology of malabsorption has not been determined by these and other investigations performed as seems indicated, the differential diagnosis then rests between gluten-induced enteropathy, idiopathic celiac disease, cystic fibrosis of the pancreas, and exudative enteropathy. The following investigations are useful in differentiating these conditions:

(1) In *gluten-induced enteropathy* serum albumen may be low, but gamma globulin is within normal limits. A moderate degree of steatorrhea is present and administration of wheat gluten leads to marked increase in fecal fat content.[51, 19, 2] According to recent studies,[39] peroral biopsy gives a suggestive histologic pattern in this condition which may persist even after effective treatment.

(2) In *idiopathic celiac disease* findings are identical to those in gluten-induced enteropathy with the exception that the characteristic response in fecal fat after ingestion of wheat gluten is absent. The findings on peroral biopsy have not been established as yet.

(3) In *cystic fibrosis* the positive sweat test, pancreatic achylia and loss of nitrogen in the stools establish the diagnosis.[17, 18] Histologic picture on peroral biopsy is apparently normal,[39] as might be expected on theoretical grounds, but not enough published evidence is available at present.

(4) In *exudative enteropathy* the low serum albumen and gamma globulin and the positive PVP test (polyvinylpyrrolidone) confirm the diagnosis.[27, 28] In the latter condition, moderate steatorrhea is present for reasons which are not clear. Because of the excessive loss of albumen in the intestinal tract, azotorrhea also may be present to a mild degree. As stated, Waldman and co-workers[49] have recently shown that lymphatic abnormalities of the intestinal wall can be demonstrated on peroral biopsy studies.

NUTRITIONAL MANAGEMENT OF MALABSORPTION (CELIAC SYNDROME) IN THE PEDIATRIC AGE GROUP

There are certain basic principles that can be applied to the nutritional management of all of the diseases causing malabsorption in the pediatric age group.

Opportune additions and modifications will naturally have to be undertaken in the treatment of the specific disease entities.

General rules for the nutritional management of this group of disorders are as follows:[19, 7, 47, 36] The diet should be high in calories, high in protein and low in fat. Simple sugars (mono and disaccharides) in general are not harmful and, indeed, are needed in order to meet the necessity for a high caloric intake. This is the main value of bananas so useful in the treatment of all of these conditions. Liberal amounts of the fat-soluble vitamins should be given in order to meet deficiencies and to compensate for the fecal loss of these nutrients. The intake of starchy products will have to be modified or restricted according to the disease entity under consideration.

The fact that general principles in dietary management are applicable to many diseases of diverse etiology and of different outlook for the patient has given rise to considerable controversy. This is primarly because it infringes the sacred principle of establishing a definite diagnosis before treatment is undertaken. Many physicians have regarded the dietary principles outlined as a "celiac diet." They have contended that many patients will be falsely labeled as having celiac disease if this diet is indiscriminately applied to individuals presenting the symptoms of malabsorption.

These objections will be met if it is realized that a diet based on the principles outlined herein is meant to counteract the effects of the impaired intestinal fat absorption common to all of the diseases causing malabsorption in the pediatric age group. This is, therefore, not a celiac diet; it is a diet for the celiac syndrome. It is a diet which is useful in the treatment of the many diseases which have a similar symptom complex although they are quite different in etiology.

It behooves the physician to undertake therapy to improve the patient's condition and in the meantime pursue all of the clinical, laboratory, and roentgenographic investigations needed in order to establish a precise diagnosis.

Dietary Treatment of Gluten-Induced Enteropathy

The cardinal principle in the treatment of gluten-induced enteropathy is complete dietary elimination of wheat or rye products.[19, 47] A glance at some of the lists of the various foods on the market,[36] usually not thought to contain wheat, reveals that wheat flour is frequently added to many commercial products. The welfare and the very life of the patients depend on the appropriate makeup of the food intake.

After the initial rapid gains in the nutritional state, further improvement is apt to be slow for a period of months or years, depending on the patient's original condition. In fact, in some cases some dietary restrictions may have to be continued indefinitely. Patience and conservatism should, therefore, be the rule in the management of this condition. Liberalizing the diet too rapidly may lead to serious and often sudden setbacks which may be more difficult to overcome than the initial episode.

Gerrard[25] has presented evidence that even patients in the so-called "latent stage" of celiac disease, who look well clinically but still have abnormal tests

relating to intestinal fat absorption, may show further striking improvement in their well being and in their rate of growth and development when dietary gluten is withheld.

Based on the dietary measures suggested by previous authors, by the more recent findings of the adverse effects of wheat and rye products,[13] and on the experience of the present authors, the management of such patients can be divided into three stages for the purposes of discussion:[19, 7, 47, 36]

Stage I — If a "celiac crisis" is present, intravenous therapy to replenish the depleted fluid and electrolyte stores must be promptly undertaken as this usually represents an acute medical emergency. The vomiting frequently present during these episodes necessitates withholding fluid or any other type of feeding by mouth. "Celiac crisis" occurs mainly in infants or small children below the age of two years and only in the ones in whom the total serum proteins are low.

Stage II — When in 24 to 48 hours the situation has improved sufficiently to permit the resumption of oral feedings, gradually a strict high-protein, low-fat, no-starch diet (no starch of any kind) is offered. Liver extract intramuscularly may be needed by sick patients at this time. After an initial period of stabilization, caloric intake will be guided by the patient's appetite and gain in weight. Duration of this very restricted regime will be from one to six months depending on the patient's condition.

Stage III — In this stage the diet can be liberalized gradually but no wheat or rye products will be allowed for a variable time up to several years. As previously mentioned from the observations of Gerrard[25] and of one of the present authors,[14] there is suggestion that some of the dietary restrictions in some cases may have to be continued indefinitely.

In our experience steroids have rarely been needed by children as their response to diet has been so satisfactory. This is in marked contrast to their frequent use in adults with sprue. When present, anemia in these children is almost always of the microcytic hypochromic variety and responds well in most instances to oral supplements of iron.

Dietary Treatment of Idiopathic Celiac Disease

There is at present little understanding about the etiology and incidence of idiopathic celiac disease. However, from a therapeutic standpoint the same dietary rules apply in *Stage I* and *II* as included in gluten-induced enteropathy. Only Stage III differs.

Stage III — In this stage all starches should be withheld from the diet for a variable period of time, depending upon the patient's rseponse and improvement. It is impossible to predict at this time how long the restrictions will have to be continued as so little is known about the true nature of this disease.

Cystic Fibrosis of the Pancreas

In therapy of cystic fibrosis antibiotic treatment of the pulmonary involvement, when present, deserves the major emphasis. It not only dominates the clinical picture but determines the fate of the patient. The nutritional status, for reasons difficult to explain, is more closely correlated in most instances to the severity of the respiratory disease than other dietary control. Although less important to the ultimate outlook, restrictions in the diet are usually needed to avoid malnutrition and vitamin deficiencies, to improve the character of the stools, and to better equip the patient to cope with the lung infection. They seldom present a serious problem in management. In the 20% of patients with cystic fibrosis but without pancreatic achylia no dietary treatment is needed.

A high caloric, high protein content of the diet is essential. These patients usually have an excellent appetite which should be a guide to their intake. Restriction of dietary fat is indicated as determined by the character of the stools. Protein is as inefficiently handled by fibrocystics as fat. Patients with this disorder, however, tolerate a greatly increased dietary intake of protein and thus maintain themselves in positive nitrogen balance.

Fat-soluble vitamins should be given in liberal amounts, pancreatic extracts are needed and additional salt is indicated during hot weather.

When pancreatic achylia is present, function of this organ will never improve because of destruction of exocrine parenchyma of the pancrease. Thus, dietary precautions will have to be observed throughout life. Fortunately, less restrictions seem to be needed with advancing age.

Other Diseases Giving Rise to the Celiac Syndrome

The general principles previously outlined for the nutritional management of the celiac syndrome will, of course, apply to all other disorders giving rise to malabsorption. In addition, specific measures will have to be undertaken to correct the basic defect responsible for the genesis of this symptom-complex in the single instance, e.g., surgical measures, treatment of the enteric infection or infestation, etc. Duration of dietary treatment will depend on rapidity and completeness of response of the basic condition responsible for the celiac syndrome.

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